REMARKS

In an Office Action mailed July 3, 2001 in the parent of this Continued Prosecution Application, the Examiner maintained rejections under 35 U.S.C. §112, first paragraph, for an alleged lack of written description supporting Claims 6-10 and for an alleged lack of enablement of Claims 1-10 and 13. The Examiner also imposed various rejections under 35 U.S.C. §112, second paragraph, for indefiniteness, insufficient antecedent basis, lack of clarity, and vagueness. The rejections were made final. Applicants respond below to each rejection and respectfully request reconsideration of the merits of this patent application.

Telephone Interview

Applicants thank the Examiner for the courtesy extended during a telephone interview with the undersigned and with inventor Kimble on November 28, 2001. Applicants acknowledge receipt of an Interview Summary mailed December 4, 2001. In the interview, Dr. Kimble explained the benefits of the invention and its advantageous use in studying effects on metalloprotease/thrombospondin ("MPT") proteins from many biological sources in a convenient nematode-based system, without regard to the functions of those MPT proteins in their native organisms. Since migration of a gonadal distal tip cell requires metalloprotease and thrombospondin domains in the protein, one can readily substitute another MPT protein in place of the native GON-1 protein and then screen for potential modulators of migration activity, with the expectation that agents that modulate of distal tip cell migration in the assay also modulate biological activities attributable to the MPT domains of the substituting protein in its native organism. Further, applicants clarified that it matters not whether the biological activities of an MPT (metalloprotease/thrombospondin) protein include cell migration in its native system. Rather, any such protein can be advantageously used in the claimed assay where it can function in place of the native GON-1 MPT protein.

In the interview, the Examiner also outlined issues relating to claim scope and language. It is believed that the Examiner's points are fully addressed in this response.

Sequence Disclosures

Applicants thank the Examiner for pointing out in the Office Action the lack of reference in the specification to the SEQ ID NO's added in applicants' prior response. By the preceding amendment to the paragraph that bridges pages 8 and 9, this objection is overcome.

Rejections Under 35 U.S.C. §112, first paragraph

Written Description:

Applicants respectfully traverse the maintained rejection of Claims 6-10. The Examiner maintained that the specification provides written description only for GON-1, murine ADAMTS-1, bovine procollagen-1 N-proteinase and human aggrecan-degrading metalloprotease but not other proteins covered by Claim 6. The Examiner also maintained that the specification does not describe what other characteristics the proteins in Claim 6 may have in addition to the metalloprotease domain and the thrombospondin domain.

Claims 6-10 further define the protein modulated in the claimed method for identifying a modulator of that protein. The protein is in the nematode and comprises a metalloprotease domain and a thrombospondin domain, as is recited in Claim 1. Claim 6 further characterizes the protein as being (i) a protein encoded by a native polynucleotide sequence, (ii) a protein encoded by a heterologous polynucleotide sequence introduced into the nematode, (iii) a protein that shares at least 20% amino acid sequence identity in the metalloprotease and thrombospondin domains with either of the foregoing and that retains functional metalloprotease and thrombospondin domains, or (iv) a chimeric protein that retains functional metalloprotease and thrombospondin domains.

Applicants satisfy the written description requirement if the specification clearly conveys to one of ordinary skill in the art that they possessed the claimed invention when the application was filed. The specification teaches that a metalloprotease domain and a thrombospondin domain are important characteristics of a protein that can direct gonadal cell migration in the claimed method (page 12 line 28 through page 14 line 33). There is a separate and detailed understanding in the art about the nature of metalloprotease and thrombospondin domains and of their characteristic sequences (page 12 line 28 through page 14 line 33). In addition, applicants mentioned three references (lines 8-17 on page 6) in the specification to reflect the state of this recognition in the art.

A skilled artisan appreciates that certain proteins are only 20% identical to GON-1 in the metalloprotease and thrombospondin domains but have sufficient attributes of metalloprotease and thrombospondin domain sequences to retain the functional characteristic of these domains. A skilled artisan can also appreciate that a chimeric protein, for example, a GON-1 derivative having its metalloprotease domain replaced by that of another protein, can retain metalloprotease and thrombospondin domain functions. The specification (first full paragraph on page 11, and page 12 line 28 through page 14 line 33) describes that these protein variants and others covered by Claim 6 can be used in the methods of the present

invention. Thus, given this familiarity with the metalloprotease and thrombospondin domain sequences, and the routine ability to mix and match domains in proteins, the specification conveyed to the skilled artisan that the applicants possessed the invention as claimed in Claim 6 when the application was filed. No other characteristics are essential to the protein or necessary to convey possession of the invention.

Rejection of Claims 1-13 for lack of enablement:

Applicants respectfully traverse the maintained rejection of Claims 1-10 and 13 for alleged lack of enablement. The Examiner stated three concerns and applicants address each below.

The first concern is that a modulator positively identified by the method of Claim 1 may not have its effect by acting on the MPT protein of Claim 1 *per se*. As was discussed during the telephone interview, Claim 1 now recites that the positively identified modulator modulates the activity of the protein. Such positively identified modulators are readily recognized, since the skilled artisan understands the need when practicing the claimed methods to distinguish between specific effects (direct or indirect) on the protein and generalized effects on the cell. The skilled artisan routinely includes proper controls to make these distinctions. The recitation of an effect in the assay on an activity of the protein is supported by the specification (e.g., paragraph bridging pages 13 and 14) and thus introduces no new matter.

Second, the Examiner seeks evidence that non-GON-1 proteins having a metalloprotease domain and a thrombospondin domain, particularly the proteins named in Claim 9, can direct gonadal cell migration in a nematode. Applicants attach a Declaration Under 37 C.F.R. §1.132 by inventor Dr. Judith Kimble to show that human aggrecan-degrading metalloprotease (aggrecanase), a protein of Claim 9 having a metalloprotease domain and a thrombospondin domain, directs gonadal cell migration in a nematode, as was predicted in the text on pages 14 and 15 of the specification. In work done at the direction of, and under the supervision of Dr. Kimble, a human aggrecanase gene was placed under control of a promoter that drives expression in the nematode gonadal distal tip cell. gon-1 mutant animals were made transgenic for the human gene, and the human gene was expressed in the distal tip cells of transgenic animals. Dr. Kimble declares that, arm extension was observed in a substantial number of transgenic animals. In contrast, no arm extension was observed in gon-1 mutant animals. This demonstrates that one can evaluate activity of non-GON-1 MPT proteins in the convenient nematode system, as claimed by the

applicants, even where directing cell migration is not a known activity of the substituting protein.

The third concern is that a protein that shares 20% identity in the metalloprotease and thrombospondin domains and a truncated form of any protein recited in Claim 6 may not function in an assay that evaluates gonadal cell migration-directing activity. As applicants discussed above in traversing the rejections under §112, first paragraph, a skilled artisan is very familiar with the attributes of metalloprotease and thrombospondin domains. For example, a skilled artisan can readily recognize from its sequence whether a protein having domains that are 20% identical in amino acid sequence to the corresponding metalloprotease and thrombospondin domains in GON-1 can retain the activity of those domains and hence can direct gonadal cell migration, because of the well-developed understanding in the art of the key amino acid residues in metalloprotease and thrombospondin domains. Along the same line, a skilled artisan can also recognize whether a truncated form of a protein recited in Claim 6 retains the activity of the characteristic metalloprotease and thrombospondin domain sequences and hence can direct gonadal cell migration. Thus, a skilled artisan can successfully select proteins covered by Claims 6-10 to practice the present invention. No undue experimentation is required. As a side note, a claim is enabled even if not every claimed embodiment is functional. Thus, even if a skilled artisan occasionally picks a non-functional protein, the present invention remains enabled. The applicants also point out that the specification envisions at the bottom of page 13 using MPT proteins that function poorly or *do not* function in the assay, specifically for identifying modulators that restore migration activity to the MPT protein. Such modulators are strong candidates for use as therapeutic agents for restoring activity *in vivo* to defective MPT proteins.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner imposed various rejections for indefiniteness, insufficient antecedent basis, lack of clarity, and vagueness. Each issue raised by the Examiner is addressed in the amended claims. Specifically, amended Claim 1 is clarified to point out that the MPT protein is in the nematode. Also in amended Claim 1, the activity of the protein has been defined as a gonadal-cell-migration-directing activity. In addition, the recited "change" in Claim 1 is clarified to be "a change in migration or shape of the developing gonadal cell attributable to modulation of the migration activity by the at least one potential modulator". This addresses the Examiner's concern that the claims reflect a modulator's effect on the migration activity, rather than a non-specific effect on the nematode or its cells. The nexus between the

preamble and method steps of Claim 1 is also clarified by positively reciting a modulation of the activity of the protein in the second step of the method.

Amended Claim 6 clarifies how different embodiments of the claim are linked to each other. Amended Claim 6 also renders moot the rejection for insufficient antecedent basis for "the polynucleotide sequence". Claim 6 is also clarified by reciting that the proteins retains functional metalloprotease and thrombospondin domains. In view of the applicants' stated intent to encompass even proteins that do not function until modulated, the term "functional" encompasses proteins that can function when modulated. The full scope of the present invention covers the chimeric proteins of Claim 6. As the Examiner acknowledged during the telephone interview, one way to practice the present invention is to employ domain swapping technology to conveniently study various metalloprotease and thrombospondin domains in the same or a similar polypeptide backbone, e.g., a GON-1 background.

The Examiner also indicated that the metes and bounds of Claim 6 are not clear because the term "sufficiently close" recited in the claim is relative. Applicants respectfully argue that the metes and bounds are clear because the claim sets forth a readily ascertainable standard, namely whether the protein is "sufficiently close" to permit the gonadal cell to migrate. This well-accepted claim format permits the applicant to encompass a full range of situations. Specifically, it is not critical here for the protein to be produced in, or to reside in, the migrating cell. Rather, the protein need only be able to have the stated effect. The protein activity can likewise be modulated in the assay whether or not it is present in the migrating cell.

Claims 7 - 9 now refer specifically to SEQ ID NO:1 and are definite and clear.

Conclusion

In view of the amendments and arguments presented above, reconsideration of the merits of this patent application is respectfully requested.

A petition for three month extension of time accompanies this filing so the CPA and this preliminary amendment will be deemed to have been timely filed. If any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055. If any additional fee is due in this or any subsequent response, please charge the fee

to the same Deposit Account.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

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Examiner: A. Shuki

For: AGENT AND METHOD FOR MODULATION OF CELL MIGRATION

File No.: 960296.95386

In the specification:

Please amend the paragraph bridging pages 8 and 9 as follows:

Fig. 1C compares the *C. elegans* GON-1 amino acid sequence (SEQ ID NO:2) to sequences of the ADAMTS-1 (SEQ ID NO:4) and PN1P (SEQ ID NO:5) proteins. In the metalloprotease domain, amino acids important for enzymatic activity are marked by an asterisk (*). Three conserved histidines (GON-1, aa 424, 428, 434) bind a catalytically essential Zn^{+2} ion in well characterized metalloproteases, while a glutamic acid residue (GON-1, aa 425) is thought to be directly involved in cleavage (Stöcker et al, 1995). In addition, two conserved glycines and a downstream methionine seem to be important for structure of the active site. GON-1 bears one of the glycines (aa 427) and the methionine (aa 454), but the second glycine is changed to serine in GON-1 (aa431). In the canonical TSPt1 domain, amino acids conserved in vertebrate TSP type-1rpeats are shown by a plus (+). The mutation, *gon-1(q518),* is marked by an inverted triangle (V). For the TSPt1-like repeats, only 2 of the 17 are shown. The consensus sequence for these repeats is: W-X_{4-5}-W-X_2-CS-X_2-CG-X_{4-5}-X-G-X_3-R-X_3-C-X_{4-27}C-X_{8-12}-C-X_{3-4}-C (SEQ ID NO:3). Because only the first two TSPt1-like motifs are shown, the other mutations are not indicated in this figure.

In the claims:

Please amend Claims 1 and 6-9 as follows:

1. (Twice amended) A method for identifying in a nematode having a developing gonadal cell a modulator of [an] a gonadal cell migration activity of a protein [for directing migration of the gonadal cell] in the nematode, wherein the protein comprises a metalloprotease domain and a thrombospondin domain, the nematode being selected from the group consisting of *C. elegans* and *C. briggsae*, the method comprising the steps of:

treating the nematode with at least one potential modulator of gonadal cell migration; and

observing in the treated nematode a change in migration or shape of the developing gonadal cell attributable to [the presence of] modulation of the migration activity by the at least one potential modulator, wherein a change in the migration or shape of the developing gonadal cell results in the identification of the modulator.

6. (Twice Amended) A method as claimed in Claim 1, the protein being selected from the group consisting of a protein encoded by a native polynucleotide sequence, a protein encoded by a heterologous polynucleotide sequence introduced into the nematode, a protein that shares at least 20% amino acid sequence identity in the metalloprotease and thrombospondin domains with either of the foregoing and that retains functional metalloprotease and thrombospondin domains, and a chimeric protein [introduced into the nematode] that retains functional metalloprotease and thrombospondin domains, the heterologous polynucleotide sequence being under transcriptional control of a promoter active in a tissue located sufficiently close to the developing gonadal cell [so as to signal] such that the protein can direct the cell to migrate.

7. (Twice amended) A method as claimed in Claim 6, wherein the native polynucleotide sequence is [*C. elegans gon-1*] SEQ ID NO:1.

8. (Twice amended) A method as claimed in Claim 6, wherein the heterologous polynucleotide sequence is a homolog of [*C. elegans gon-1*] SEQ ID NO:1.

9. (Amended) A method as claimed in Claim 8 wherein the homolog of [*C. elegans gon-1*] SEQ ID NO:1 encodes a metalloprotease enzyme selected from the group consisting of murine ADAMTS-1 protein, bovine procollagen-1 N-proteinase, and human aggrecan-degrading metalloprotease.